IMMUNE SYSTEM I
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Reading: Gartner & Hiatt, Chapter 9; Sheedlo Chapter 12, p109

Learning Objectives:
- Identify the organs and tissues that comprise the lymphoid system.
- Know the functions of the lymphatic system.
- Describe the histologic organization of the thymus.
- Describe the histologic organization of the lymph node.

Key Words: Lymphocytes, Lymphatic Circulation, Cortex, Medulla, Thymus, Hassall's Corpuscles, Lymph Node, High Endothelial Venule (HEV)
I. BASIC INFORMATION
   A. Lymphatic and lymphoid -- tissues or organs in which lymphocytes form the major cellular component.
   B. Includes:
      1. Thymus
      2. Lymph nodes
      3. Spleen
      4. Lymphoid nodules: tonsils, appendix, Peyer's patches in ileum, as well as small collections of lymphoid tissue throughout the GI, respiratory, and urinary tracts (termed Mucosa-Associated Lymphoid Tissue or MALT).
   C. All lymphoid organs originate from mesoderm, EXCEPT the thymus that originates from mesoderm and endoderm.
   D. Function is surveillance and defense (“immunity”)

II. LYMPHOID TISSUE AND THE IMMUNE RESPONSE
   A. Specialized form of connective tissue containing large numbers of lymphocytes. Reticular cells and reticular fibers make up the supporting network
   B. Types of lymphocytes
      1. T-lymphocytes or T-cells. Mediate cellular immunity (protect against microorganisms, tumor cells, and viruses).
      2. B-lymphocytes or B-cells. Mediate humoral immunity through production of antibodies (or immunoglobulins).
   C. Both T- and B-lymphocytes originate from stem cells in the bone marrow.
      1. Maturation site for T-cells is the thymus.
      2. Maturation site for B-cells is uncertain. In birds, the B-cell maturation site is the bursa of Fabricius. The bursa equivalent in man may be the bone marrow or gut-related lymphoid tissue.
      3. All lymphocytes express glycoproteins on their surface membranes. These surface markers are named according to an international classification: CD (Cluster Designation or Cluster of Differentiation) system.
D. B-lymphocytes

1. When come into contact with antigen, proliferate and differentiate into **plasma cells**. Plasma cells secrete **immunoglobulins**.

2. A small percentage of activated B-cells transform into **memory B cells** that are pre-programmed to respond rapidly to a subsequent exposure with the same antigen.
E. T-lymphocytes
1. When come into contact with antigen, transform into activated T-cells. Two primary subpopulations of T-lymphocytes:
   a. **T-Helper cells**: Secrete a variety of cytokines that coordinate cell-mediated as well as humoral immunity. These cells are $\text{CD}4^+$
   b. **T-Suppressor/Cytotoxic cells**: Function in the killing of some malignant cells, foreign cells, and virus-infected cells. Also suppress the activity of B-cells, thereby curbing the response to foreign antigens and one's own (self) antigens. These cells are $\text{CD}8^+$.

F. Natural killer (NK) lymphocytes
1. 10-15% of circulating lymphocytes. Main function is to kill virus-infected cells and cancer cells.

G. Antigen-presenting cells (APCs)
1. Responsible for processing antigen and "presenting" it to lymphocytes. Derived from the bone marrow and belong to the **mononuclear phagocyte system (MPS)**.
2. Include macrophages, Kupffer cells (liver), Langerhans cells (skin), dendritic cells present in lymphoid organs, and epithelial cells of the thymus.

III. LYMPHATIC CIRCULATION
A. Composed of vessels that remove excess extracellular fluid (lymph) from spaces between tissues and return it to the cardiovascular system. Most numerous under the skin and in mucous membranes. Are **not present** in the central nervous system, eye, ear, cartilage or bone.
1. Begin as blind-ended vessels in tissues. Walls of these vessels are more permeable than walls of capillaries, so cells and foreign substances pass readily into the "lymph."
2. Lymphatic vessels empty into the **thoracic duct** which joins the venous system at the junction of the internal jugular and subclavian veins. Lymphocytes that were in the lymph fluid now become components of blood.

B. Lymph passes through various **lymphoid organs** (primarily lymph nodes) where antigens are concentrated and presented to lymphocytes, ultimately leading to an immune response.
1. Lymph enters lymph node through **afferent lymphatics** and leaves via **efferent lymphatics**. Some lymphocytes will remain in the B-dependent or T-dependent areas of the lymph node.
2. Lymphocytes regain entry into the lymphatic system via **postcapillary venules** (also called high endothelial venules or HEVs) in the lymph nodes.
3. This recirculation of lymphocytes involves all lymphatic tissue **except** the thymus and bone marrow.
IV. THYMUS

A. Bilobed lymphoid organ in the mediastinum. Progressively atrophies from puberty to old age and is partially replaced by fat and connective tissue. Is a T-cell dependent organ.

B. Has a thin loose connective tissue capsule that penetrates into the parenchyma, dividing the organ into lobules. Each lobule has a cortex and medulla.
   1. Connective tissue contains blood vessels, efferent lymphatic vessels (NO afferent lymphatics), and nerves.

C. Cortex
   1. Composed of many closely packed, small pre-T-lymphocytes, epithelial reticular cells, and macrophages. There are NO lymphoid nodules or follicles.
   2. Epithelial reticular cells are connected to each other via desmosomes at the end of long cytoplasmic processes.
   3. Immature T-lymphocytes (thymocytes) are produced and accumulate in the cortex. Most will die here; the surviving cells will migrate to the medulla where they acquire their CD markers, enter the bloodstream through venules, and migrate to the T-dependent areas of other lymphoid organs (paracortical area of lymph nodes, PALS of the spleen, some parts of Peyer’s patches) where they complete the maturation process.

D. Medulla
   1. Contains a large number of epithelial reticular cells, some large immature T-lymphocytes, and macrophages.
   2. Contains Hassall's corpuscles. Composed of flattened epithelial reticular cells which have degenerated; they may show some keratinization. Arranged in a concentric formation and vary in size. Function is unknown.
E. Thymic function

1. Essential for the development of T-lymphocytes. Produces several growth factors (thymosin, thymotaxin, thymopoietin, serum thymic factor) that stimulate proliferation and differentiation of T-lymphocytes.
2. Most of the growth factors are thought to be produced by the epithelial reticular cells.

V. LYMPH NODES

A. Lymphoid organs distributed throughout body along the lymphatic vessel system.
   1. All lymph passes through at least one node before it enters the circulatory system.
   2. Afferent lymphatic vessels enter the LN along the convex surface of the capsule. Efferent lymphatic vessels leave the LN at the hilum. Arteries enter and veins leave the node via the hilum.
   3. Dense connective tissue capsule that sends connective tissue septae or trabeculae into the node. Reticular cells and reticular fibers form a supporting meshwork that extends throughout the parenchyma.
   4. The parenchyma consists of diffuse and nodular lymphoid tissue and is separated into an inner and outer cortex and a medulla.

B. Lymph Flow
   1. Afferent lymphatic vessels → subcapsular sinus → cortical (intermediate) sinuses → medullary sinuses → efferent lymphatic vessels.
   2. Lymphatic vessels contain one-way valves to assure flow of lymph in the proper direction.
C. Cortex

1. **Subcapsular** sinus located immediately beneath the capsule. Empties into the medullary sinuses via the cortical (also called paratrabecular or intermediate) sinuses that run alongside the connective tissue trabeculae.

2. **Outer cortex** is meshwork of diffuse lymphoid tissue with macrophages, T-lymphocytes, plasma cells, and reticular cells. Contains lymphoid nodules (follicles) composed of B-lymphocytes.

3. **Inner (or deep) cortex** is continuation of the outer cortex and contains diffusely arranged T-lymphocytes. Also called the paracortex or paracortical zone. Few, if any, lymphoid nodules are found.
   a. Contains specialized vessels called high endothelial venules (HEVs). Are lined with cuboidal endothelial cells with large nuclei, and serve as the point of entry for lymphocytes from peripheral blood into LN parenchyma.

D. Follicles

1. **Primary follicles** contain small B-lymphocytes.

2. **Secondary follicle** has a pale central area, the germinal center. Germinal center contains activated B-cells that will give rise to plasma cells. Germinal center is surrounded by a cuff of small B-lymphocytes called the mantle zone. The presence of germinal centers indicates the lymph node is antigenically-stimulated.
3. Germinal center contains **Dendritic Reticulum Cells** (DRCs) which trap antigens and present them to B-cells. Are long-lived and difficult to see by light microscopy.

4. **B-cells** in the germinal center are large with vesicular nuclei. These are proliferating cells; mitotic figures are not uncommon.

5. **Tingible body macrophages** can be found. Are large cells whose cytoplasm contains phagocytized debris. Cytoplasm is not conspicuous, so appear as "clear areas" in the tissue.

E. Medulla
   1. Composed of **medullary cords** separated by **medullary sinuses** that contain lymph, lymphocytes, and macrophages.
   2. Medullary cords contain primarily B-lymphocytes, macrophages, plasma cells, and reticular cells. Major site of phagocytosis and immunoglobulin synthesis.

F. Lymph node function
   1. **Main function is to filter lymph** before it returns to the circulatory system. Phagocytic cells within the lymph node will remove foreign particles and bacteria. Foreign antigens become trapped on the surface of the APCs and then presented to memory B-cells.
   2. B-cells may recognize the antigen with or without the assistance of T-cells. Activated B-cells migrate to the germinal center of the follicles and begin multiple mitotic divisions that eventually give rise to immature **lymphoblasts**.
   3. Lymphoblasts give rise to **plasma cells** and **memory B-cells**. Plasma cells migrate to medullary cords where they begin synthesizing antibodies. Memory B-cells circulate to various areas of the body and set up housekeeping, waiting for the antigen to reappear.
   4. **T lymphocytes** can become activated with eventual dissemination of cytotoxic T-cells throughout the body.
   5. Lymph nodes that contain cells responding to an antigenic load typically become **enlarged** due to formation of germinal centers and proliferation of B-lymphocytes.